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Does IgA antibody against β2 glycoprotein I increase cardiovascular risk in hemodialysis patients?

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Cardiovascular disease is the most common cause of mortality in patients with chronic kidney disease on hemodialysis. In addition to a high prevalence of traditional cardiovascular risk factors, other specific factors, including uremia and chronic inflammation, seem to contribute to the excess cardiovascular mortality. The findings of Serrano *et al.* point to a link between IgA antibodies against β2 glycoprotein I and cardiovascular events in renal dialysis patients.

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The risk of cardiovascular disease is high in patients with chronic kidney disease, and cardiovascular disease accounts for up to 50% of deaths in this population. In the subset of patients receiving hemodialysis the rate of cardiovascular mortality is 10–to 20–fold higher than that of the general population.[1] In addition to a high prevalence of traditional cardiovascular risk factors in patients with chronic renal disease (for example, hypertension and diabetes mellitus), other specific risk factors, including degree of uremia, comorbidity, inflammatory response, hypoalbuminemia, and hyperparathyroidism, also seem to contribute to the excess cardiovascular risk.

The antiphospholipid syndrome (APS) is an acquired, strongly prothrombotic disease characterized by arterial and venous thromboembolism and/or pregnancy morbidity in the presence of persistent high-titer autoantibodies directed against a broad range of phospholipids and phospholipid-binding proteins.[2] The history of APS dates back to reports in the 1950 s of false-positive laboratory test results for syphilis in patients who went on to develop systemic lupus erythematosus (SLE). It became apparent that Wasserman *et al.* had detected the earliest anti-phospholipid antibodies in 1906 with the development of a complement-fixation assay for syphilis using phospholipid antigen from hepatic extract of fetuses with congenital syphilis.[3] This phospholipid antigen was later named 'cardiolipin' (as subsequently mitochondrial phospholipids were extracted from bovine heart muscle), and anti-cardiolipin antibody detection became the basis of the current-day Venereal Disease Research Laboratory (VDRL) test for syphilis. Widespread screening of donated blood for syphilis led to the realization that some patients with SLE possessed anti-phospholipid antibodies resulting in false-positive VDRL tests, prolonged laboratory clotting times, and strong predisposition to thrombosis.

Anti-phospholipid antibodies are detected either by a prolongation of phospholipid-dependent coagulation tests (lupus anticoagulant) or by solid-phase immune assays. They are a heterogeneous group of autoantibodies directed against a variety of different antigens (including prothrombin, annexin V, protein C, and protein S); it is thought that binding of these antigens is at least partly responsible for the prothrombotic phenotype of APS. In the early 1990s, several groups reported that a proportion of anti-cardiolipin antibodies were directed against the phospholipid cofactor β2 glycoprotein I (β2GPI). This single-chain polypeptide glycoprotein is a 50–kDa plasma apolipoprotein (plasma concentration 200 μg/ml) that binds anionic phospholipids; it is required for anti-phospholipid antibody binding in a subset of patients with SLE

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Table 1 | Laboratory tests for APS: comparison of Sapporo[6] and Sydney[7] criteria

	Sapporo (1999)	Sydney (2006)
Lupus anticoagulant	Positive on two or more occasions at least 6 weeks apart	Positive on two or more occasions at least 12 weeks apart
Anti-cardiolipin antibodies	Detection by standardized β2GPI ELISA	Detection by standardized ELISA
	IgG and/or IgM of medium or high titer	IgG and/or IgM of medium or high titer (>40 units IgG or IgM titer or >99th percentile)
	Positive on two or more occasions at least 6 weeks apart	Positive on two or more occasions at least 12 weeks apart
Anti-β2GPI antibodies	Not included	IgG and/or IgM titer >99th percentile Positive on two or more occasions at least 12 weeks apart

Abbreviations: β2GPI, β2 glycoprotein I; APS, antiphospholipid syndrome; ELISA, enzyme-linked immunosorbent assay.

and APS.[4] β2GPI is an abundant circulating protein synthesized by hepatocytes; although its precise physiological role remains unclear, β2GPI seems to have a function both in modulating platelet activation and in innate immune defenses, including removal of cellular waste and microparticles. The immune function seems to be related to the structural conformation of the protein, which exists in at least two different forms ('circular' and active 'open' forms). It is thought that β2GPI antibody formation might be related to the conformation change in the antigen seen in the presence of infection.[5] β2GPI in the circulation exists in the 'circular' conformation where the epitopes for autoantibodies are hidden; exposure of these cryptic epitopes is then necessary for formation of anti-β2GPI antibodies. β2GPI is now recognized as the major antigen for anti-phospholipid antibodies in APS; autoantibodies against β2GPI (particularly IgG against the N-terminal part of β2, domain I) are strongly associated with both thrombosis and the other clinical features of the syndrome.

β2GPI has been identified in atheromatous plaques, and it is thought that antibodies directed against β2GPI may have a role in accelerated atherosclerosis.[5] Circulating oxidized low-density lipoprotein–β2GPI complexes have been detected in patients with SLE and in APS, which suggests a role for these in autoimmune-related atherosclerosis; however, it is unclear whether this accelerated atherosclerosis is a consequence of underlying autoimmune disease rather than specifically due to β2GPI antibody in these patients. Anti-phospholipid antibody has also been associated with accelerated atherosclerosis in murine models, in which infused antibody or induction of antibody against murine β2GPI led to increased atherosclerotic plaque formation.[5] β2GPI antibodies have been shown to cause endothelial dysfunction *in vitro*, producing an inflammatory and prothrombotic phenotype including cross-reactivity with oxidized low-density lipoproteins.

The diagnosis of APS is based on strict clinical and laboratory criteria. Consensus guidance for APS diagnosis (the 'Sapporo criteria')[6] was published in 1999; the revised 2006 'Sydney criteria' saw the inclusion of antibodies against β2GPI as part of the diagnostic algorithm (Table 1).[7] Although APS may affect any organ, the current clinical diagnostic criteria are restricted to pregnancy loss and/or thromboembolism. Venous thrombosis (deep vein thrombosis and pulmonary embolism) is the most frequent clinical manifestation of APS, occurring in up to 55% of patients; arterial thromboembolism is less common and manifests mostly as stroke and coronary ischemia. Notably, the current diagnostic laboratory criteria include only IgG and IgM antibody positivity to cardiolipin and/or β2GPI, although the IgM isotype is less frequently associated with clinical features of APS. IgA antiphospholipid antibody does not appear in either of the diagnostic classifications; the authors of the Sydney criteria did not consider there to be sufficient evidence at the time to include isolated IgA anti-β2GPI positivity in the laboratory diagnosis of APS.

The case for the clinical relevance of IgA anti-β2GPI is supported by the single-center study by Serrano and co-workers[8] (this issue), which reports the prevalence of anti-cardiolipin and anti-β2GPI antibodies in a group of 124 patients on hemodialysis for end-stage renal disease. Interestingly, almost one-third of these patients were positive for IgA anti-β2GPI, and these subjects had significantly higher overall mortality, cardiovascular mortality, and thrombotic event rate. An increased prevalence of both arteriovenous fistula (AVF) and non-AVF thrombosis was seen in this group. It is noteworthy that the majority of subjects possessing IgA anti-β2GPI did not have a diagnosis of underlying autoimmune disease (with just above one-third reported as having a diagnosis of diabetic nephropathy) and were not of an African-American background (in which an increased incidence of IgA anti-β2GPI is well recognized). Data on lupus anticoagulants are not presented, which is surprising given their particularly strong association with thromboembolism in APS. The reason for generation of IgA anti-β2GPI in dialysis patients is unclear, but the authors speculate that binding of circulating β2GPI to dialysis membranes might reveal a neoepitope for antibody binding, resulting in a prothrombotic phenotype; it would be of interest to identify the β2GPI domain to which antibodies were directed in these subjects. The investigators suggest that testing dialysis patients for IgA anti-β2GPI antibodies might identify a subgroup of dialysis patients at increased risk of adverse cardiovascular events who might benefit from additional therapeutic intervention and also from revision of the laboratory diagnostic criteria for APS. However, given the relatively small number of patients in this study (and the varied types of vascular pathology reported), these findings require confirmation in larger multicenter studies.

In most cases of APS, IgA anti-phospholipid antibodies are found in the presence of other isotypes.[7] There are, however, a limited number of reports in the literature of patients (with and without lupus) with clinical features of APS (including recurrent pregnancy loss, stroke, and myocardial infarction) and isolated IgA anti-β2GPI positivity.[9,10] IgA anti-cardiolipin antibody has been associated with ischemia in patients with coronary artery disease and has also been reported to be predictive of onset and outcome of acute coronary syndrome including unstable angina and ST-elevation myocardial infarction. Although IgA anti-β2GPI antibodies are not currently part of the diagnostic criteria for APS, they are reported to appear more frequently in certain groups, including African-American patients with SLE and obstetric patients with lupus and APS. Thus there is growing evidence that IgA anti-β2GPI testing might identify a small subset of patients with APS falling outside the Sydney criteria for APS, and that it may therefore be appropriate to test for IgA anti-β2GPI in patients with clinical features of APS who are negative for the currently recommended laboratory tests. The report of a high prevalence of isolated IgA anti-β2GPI in renal dialysis is intriguing; although this finding requires validation in larger future studies, it strengthens the case for an improved laboratory and clinical classification of APS. There are, after all, more than 25 different autoantibodies described in APS directed against phospholipids and/or phospholipid-binding proteins with differing pathogenicities. Multiple potential pathogenic mechanisms for thrombosis may be present in APS; a frequent characteristic in APS patients is platelet activation, which may have a key role in thrombosis in addition to other potential mechanisms, including inhibition of anticoagulation, reduced fibrinolysis, and direct effects on endothelium. No doubt the diagnostic clinical and laboratory criteria for this heterogeneous disease will continue to evolve; for now it is too early to recommend routine testing for IgA anti-β2GPI in renal patients on the basis of a single study.

DISCLOSURE
The authors declared no competing interests.

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